A convenient synthesis of cyclopenta[b]pyridin-2,5-dione as a non- glycosidic cardiotonic agent

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Dedicated to Professor Guy Quéguiner on the occasion of his 70th birthday

Abstract
A straightforward synthesis of cyclopenta[*b*]pyridin-2,5-dione is reported starting from the commercially available 2-bromo-6-methoxypyridine. The overall route consists in a first sequence of regioselective ortho lithiation and methoxycarbonylation followed by Heck vinylation, alkene reduction, cyclization and decarboxylation.

Keywords: Lithiation, Heck vinylation, pyridine, cyclopenta[*b*]pyridine-2,5-dione

Introduction

A recent pharmacological evaluation of various functionalized 2-pyridones as cardiotonic agents has revealed that the cyclopenta[*b*]pyridin-2,5-dione (**1**) displays a high activity rather similar to Milrinone (**2**) which is the most effective non glycosidic cardiotonic agent clinically used for the treatment of severe heart failure.[1] Cyclopenta[*b*]pyridin-2,5-dione (**1**) constitutes also an interesting tensor of pharmaceutics exemplified by the antibacterial product **5** and a building-block for the access to 2-cyclopenta[*b*]pyridin-5-one (**3**) as seco analogues of 8-azasteroids (**4**).[2]

Results and Discussion

Despite the fact that the cyclopenta[*b*]pyridin-2,5-dione **(1)** is gaining interest as biologically active compounds and valuable building-blocks only two methods of preparation could be found in the literature. The first synthesis of cyclopenta[*b*]pyridin-2,5-dione (**1**) was first reported in 1954 (6 steps synthesis and a 13 % overall yield).[3] Mosti and his team published in 2003 a novel synthetic route based upon a one-pot and two-step construction of the 2-pyridone ring from the cyclopenta-1,3-dione.[1] We recently described a novel synthesis of 6-methyl cyclopenta[*b*]pyridin-5-one (**8**) based on Heck vinylation of 2-bromo-6-methyl nicotinate (**6**) with methacrylate affording the pyridylacrylate intermediate **7**, alkene reduction and Dieckmann condensation as depicted in Scheme 1.[4] We wish to report here our results on the application of the latter method to the preparation of the cyclopenta[*b*]pyridin-2,5-dione (**1**). Our retrosynthetic analysis suggests that 2-bromo-6-methoxynicotinate (**10**) could be a valuable precursor for this purpose (scheme 1). The pyridylacrylate **9** could be first prepared by Heck vinylation of bromopyridine **10**. The expected cyclopenta[b]pyridin-2,5-dione (**1)** would be then obtained by reduction of the alkene followed by a cyclization-decarboxylation sequence. The success of this novel approach mainly depends on the access to the unknown 2-bromo-6-methoxynicotinate **10**. Two possible routes could be designed: (i) the regioselective displacement of a bromine atom at position 2 of the methyl 2,6-dibromonicotinate (**11**) which could be readily prepared in two steps from the 2,6-dichloronicotinic acid by bromination and esterification[7] or (ii), the regioselective methoxycarbonylation of the commercially available 2-bromo-6-methoxypyridine (**12**).

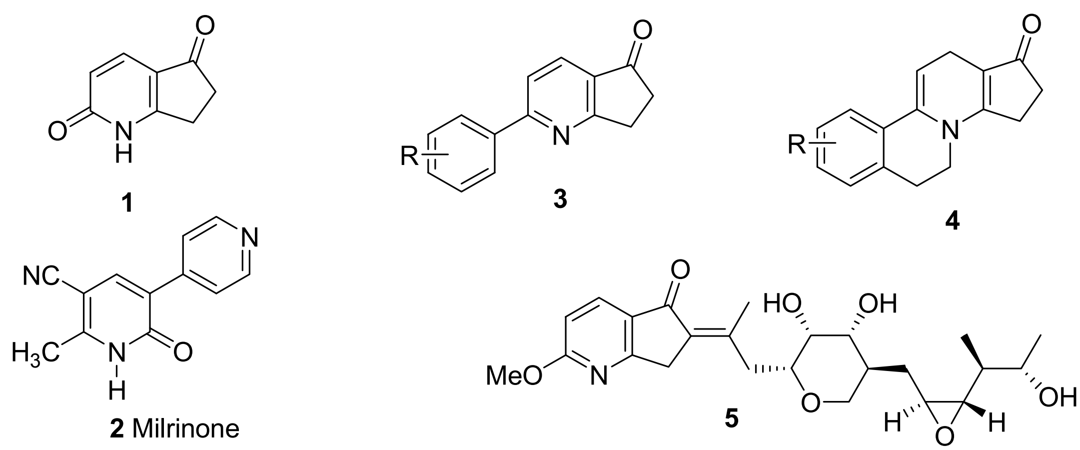
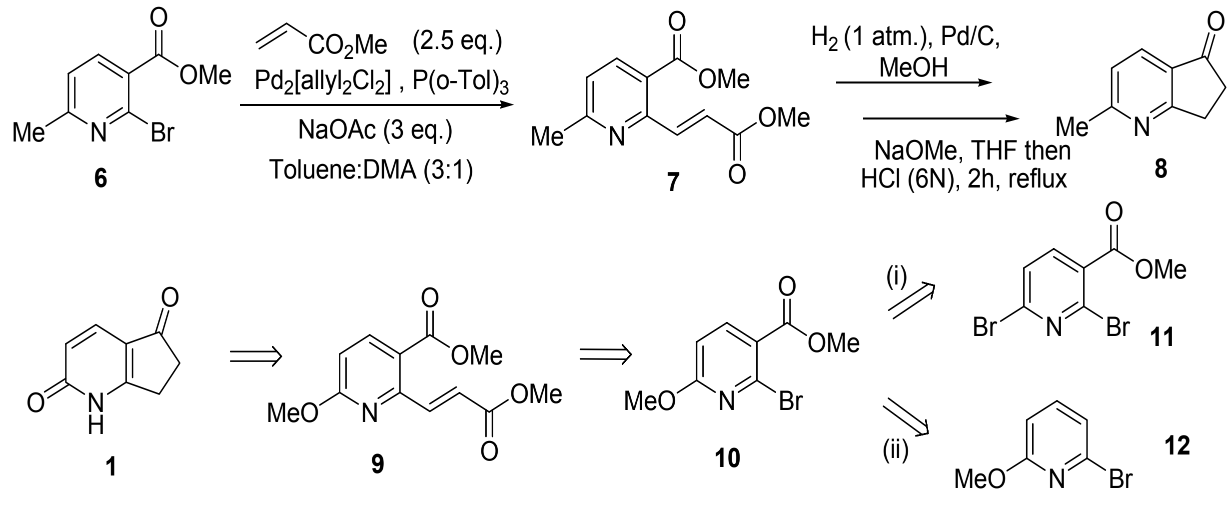
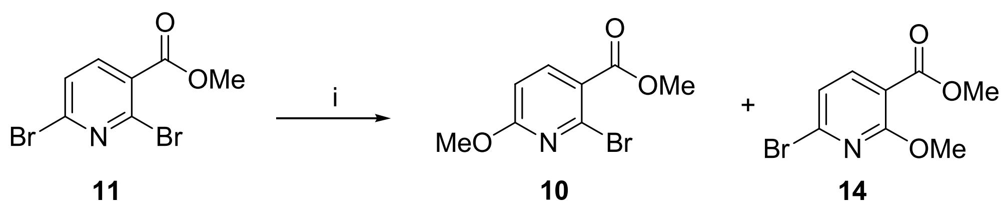


Figure 1



Scheme 1. Previously reported synthesis of 6-methylcyclopenta[b]pyridine-5-one (**8**) and retrosynthetic analysis of cyclopenta[b]pyridin-2,5-dione (**1**).

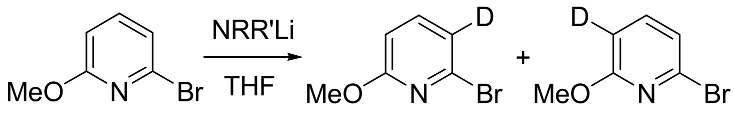
We first attempted to displace the bromine atom at position 2 of ethyl 2,6-dibromonicotinate (**11**) with sodium methoxide. Treatment of **11** with 1.5 equivalent of sodium methoxide was carried out in refluxing MeOH for 24h following the Hirokawa's protocol.[5] A complete conversion of the starting material was observed and a mixture of 2- and 6- monosubstituted products **10** and **14** in a 7:3 ratio (^{1}H NMR) could be obtained in 75 % yield. Unfortunately, the two regioisomers **10** and **14** could not be separated by chromatography. Moreover, replacement of sodium methoxide by potassium methoxide also led to a 1:1 mixture regioisomers **10** and **14**.



Scheme 2. *Reagents and conditions*: (i) MeONa (1 equiv.), MeOH, reflux, 24h, 75%.

We then shifted to the second route based on the regioselective methoxycarbonylation at position 3 of 2-bromo-6-methoxy pyridine (**12**). To this purpose, we first examined the lithiation of 2-bromo-6-methoxy pyridine (**12**) by treatment with hard bases such as lithium amides in THF before quenching the lithio intermediates with D_2O (Table 1). A first set of lithiation experiments was achieved using 2,2',6,6'-tetramethylpiperidinyl-lithium (LTMP) at -78 °C (entries 1-3).

Table 1. Assays of regioselective lithiation of **12** with lithium amides

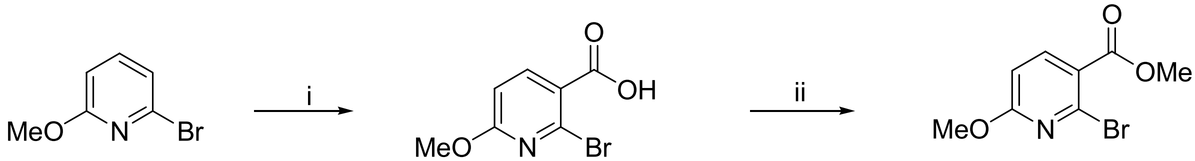


12 **15a** **15b**

Entry	Base	Equiv.	T (°C)	**15a** (%)[a]	**15b** (%)[a]
1		1	-78°C	-	-
2	LTMP	2	-78	0	64
3		3	°C	10	80
			-78°C		
4		2	-78	15	-
5	LDA	3	°C	15	-
			-78°C		
6		2	-50	22	12
7		3	°C	20	11
			-50°C		

[a] The ratio was determined by ^{1}H NMR spectroscopy

No deuterated product was obtained using 1 equivalent of LTMP whereas the 5-deuterated compound **15b** was selectively formed in 64% yield using 2 equivalents of LTMP. The starting material conversion could be significantly improved employing 3 equivalents of LTMP leading to a mixture of 3- and 5-deuterated products (**15a, 15b**) in 2:8 ratio in favor of the **15b** isomer. The less hard lithium diisopropylamine (LDA) was also checked (entries 4-7). Treatment of **12** with 2 equivalents of LDA followed by D_2O trapping specifically provided the 3-deuterated product **15a** in 15 % yield (entry 4). This result could be related to the higher acidity of the proton at position 3. Surprisingly, we observed that the yield of 3-deuterated compound **15a** was not improved using 3 equivalents of LDA at the same temperature (entry 5). Moreover warming the 3-lithio anion from -78°C to -50 °C[6] before trapping with D_2O afforded a mixture of **15a** and **15b** (entries 6,7).

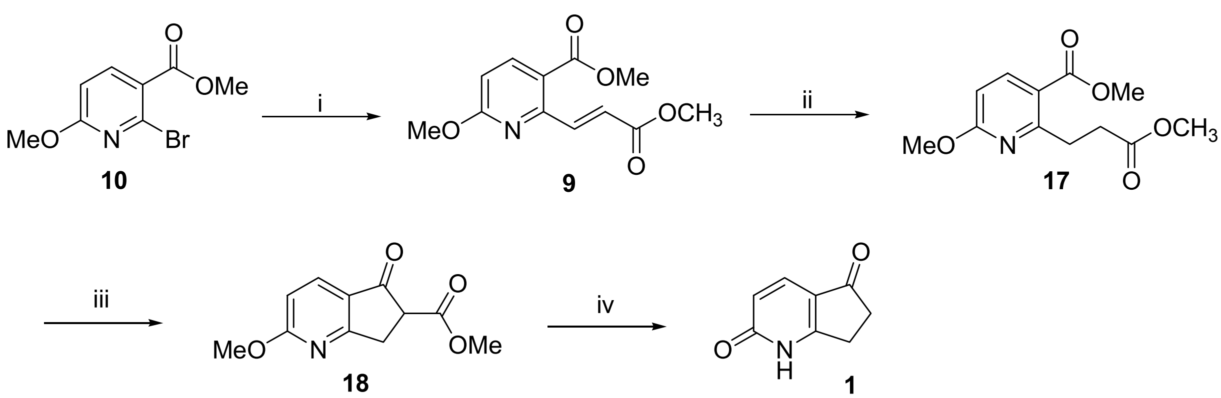


12 **16** **10**

Scheme 3. *Reagents and conditions*: (i) (a) LDA (2 equiv.), -78°C, THF, 1h, (b) solid carbon dioxide, (c) HCl (2*M*), 13 %; (ii) (a) $(COCl)_2$, DMFcat., (b) MeOH, 92%.

The 3-lithio anion formed by treatment of **12** with 2 equivalents of LDA at -78°C in THF (table 1-entry 4) did not react with methyl cyanoformate but could be trapped by carbon dioxide to give the 3-bromo-6-methoxynicotinic acid (**16**) after acidic treatment. Acid (**16**) was isolated in 13 % yield but the unreacted starting material **12** could be was readily recovered and re-used. Finally **16** was obtained in 41 % overall yield after five lithiation–carboxylation sequences. Esterification of **16** gave the expected methyl 2-bromo-6-methoxy nicotinate (**10**) in 92 % yield.

Heck vinylation of **10** with methyl acrylate using the η^3-allylpalladium chloride dimer with P(*o*-Tol)$_3$ complex as catalyst in toluene and dimethylacetamide (DMA) as co-solvent[4] provided the β-2-pyridyl acrylate **9** in an excellent 82% yield. The use of DMA is a crucial parameter as the vinylation of **10** failed without this co-solvent. Reduction of the alkene under soft conditions provided diester **17** which could be cyclized by a Dieckmann condensation with sodium methoxide to methyl cyclopenta[b]pyridine-5-one-6-carboxylate (**18**) in 70% overall yield. Finally, treatment with hydrochloric acid allows hydrolysis, decarboxylation and demethylation of **18** to give cyclopenta[c]pyridine-2,5-dione (**1**) in 84 % yield.



Scheme 4. *Reagents and conditions*: (i) methyl acrylate (2.5 equiv.), $Pd_2[allyl_2Cl_2]$, P(*o*-Tol)$_3$, NaOAc (3 equiv.), toluene: DMA (3:1), 92%; (ii) H_2 (1 atm), Pd/C (10 mol %), MeOH, r.t., 2h, 93%; (iii) NaOMe, THF, reflux, 2h, 75%; (iv) HCl (5 M), reflux, 3h, 84%.

Conclusions

A convenient route to cyclopenta[*b*]pyridin-2,5-dione (**1**) is reported starting from methyl 2-bromo-6-methoxynicotinate (**10**) through a 4 steps synthesis, vinylation, alkene reduction and cyclization-decarboxylation, in 48% overall yield. Two routes were studied for the previous preparation of the parent methyl 2-bromo-6-methoxynicotinate (**10**). Regioselective displacement of the bromine atom of methyl 2,6-dibromonicotinate (**11**) by the sodium or potassium methoxide could not be applied leading to a mixture of regioisomers which could not be separated by chromatography. The second approach was based upon the regioselective carboxylation of the commercially available 2-bromo-6-methoxypyridine (**12**) at position 3 of the pyridine nucleus. The regioselective lithiation-carboxylation and esterification of **12** at position 3 was achieved using LDA at -78°C in THF to give the expected methyl 2-bromo-6-methoxynicotinate (**10**) in 12 % yield in two steps.

Experimental Section

General Procedures. Tetrahydrofuran (THF), ether (Et_2O) were pre-dried with pellets of KOH and distilled over sodium benzophenone ketyl under Ar before use. CH_2Cl_2, NEt_3 and toluene were distilled from CaH_2. Methanol and ethanol were distilled from magnesium turnings; dimethylacetamide was distilled over 4 A molecular sieves. For Flash chromatography, Merck silica gel (70-230 mesh) was used. The melting points were measured on a Kofler melting points apparatus and were not corrected. The ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker Avance-300 spectrometer operating at 300 MHz. Commercially available starting materials were used without further purification. Infrared spectra were recorded on a Perkin-Elmer FT-IR 1650 spectrophotometer. Elemental analysis of compounds was carried out on a Carlo Erba 1160. Mass spectra were recorded on a JEOL JMS AX-500 spectrometer, in electronic impact (EI). The starting compound **12** is commercially available.

Preparation of 6-methoxy-2-bromonicotinate (10)

Methyl 2,6-dibromonicotinate (11**).** To a stirred solution of 2,6-dibromonicotinic acid[7] (500 mg, 1.8 mmol) and 3 drops of DMF in dry CH_2Cl_2 (10 ml) was slowly added oxalyl chloride (172 μL, 2.0 mmol) at 0°C. The mixture was stirred at room temperature for 1h and solvents were removed *in vacuo*. To the crude product was added dry methanol (10 ml) at 0 °C and the resulting solution was stirred for 2 h at room temperature. Methanol was removed *in vacuo* and the crude solid was dissolved in CH_2Cl_2 (10 ml). The pH of the aqueous layer was then adjusted to 7 by adding aq. K_2CO_3 (2*M*). The separated organic layer was washed three times with water, dried ($MgSO_4$) and concentrated *in vacuo* to give **11** (488 mg, 92 % yield) as beige powder, mp = 51-52 °C; IR (KBr) υ 3093, 2957, 1728, 1567, 1416; ^1H NMR ($CDCl_3$) δ 3.93 (s 3H), 7.52 (d, 1H, J = 8.1 Hz), 7.93 (d, 1H, J = 8.1 Hz; ^{13}C NMR ($CDCl_3$) δ 53.5, 127.3, 128.7, 140.4, 141.7, 143.9, 165.0; Anal. Calcd for $C_7H_5Br_2NO_2$ (294.9): C, 28.51; H, 1.71; N, 4.75. Found: C, 29.01; H, 1.67; N, 4.71 %.

Procedure for nucleophilic substitution using sodium methoxide. To a stirred solution of methyl 2,6-dibromonicotinate (**11,** 1.5 g, 5.0 mmol) in dry MeOH (20 ml) was added NaOMe (270 mg, 5.0 mmol). The mixture was refluxed for 24 h and then poured into cold aq. $NaHCO_3$ (5 %, 50 ml) and the product was extracted with ether (3x20 mL). The separated organic phase was separated and concentrated *in vacuo*. Ether (40 mL) was added to the crude liquid and the organic phase was washed with brine (40 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (CH_2Cl_2) to give a (7:3) mixture of **10** and **14** (923 mg, 75 %).

2-Bromo-6-methoxypyridine (12). To a stirred solution of 2,6-dibromopyridine (20 g, 84 mmol) in dry MeOH (50 mL) was added NaOMe (8g, 148 mmol). The mixture was refluxed for 25 h and then poured into a cold aq. soln. of $NaHCO_3$ (5%, 50 mL). The product was extracted with ether (3x30 ml) and the combined organic layers were washed with brine (40 ml) and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (EtOAc/Petrol 9:1) to give **12** (13 g, 83 %) as a liquid; bp=206-207°C; IR (KBr) υ 2953, 1596, 1582, 1558, 1472, 1413, 1298, 1022, 857; ^{1}H NMR ($CDCl_3$) δ 3.93 (s 3H), 6.69 (t, 1H, *J* = 7.7 Hz), 7.06 (d, 1H, *J* =7.7 Hz), 7.40 (d, 1H, *J* = 7.7 Hz).

2-Bromo-6-methoxynicotinic acid (16). To a stirred solution of LDA (106 mmol) in dry THF (50 mL) was added dropwise under N_2 at –78°C a solution of 2-bromo-6-methoxypyridine **12** (10 g, 53 mmol) in dry THF (50 ml). After stirring 1 h. at the same temperature, the mixture was poured on an excess of carbonic dry ice. Solvents were removed *in vacuo* and the crude residue was dissolved in water (30 ml). The separated aqueous layer was washed with CH_2Cl_2 (3x15 ml) and pH was adjusted to 4 by adding aq. HCl (2*M*). The product was extracted with CH_2Cl_2 (3x15 ml) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give **16** (1.6 g ,13 %) as a beige solid; mp= 212-213°C; IR (KBr) ν 1302, 1591, 1693, 2959, 3418; ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H), 6.91 (d, 1H, *J* = 8.4 Hz), 8.10 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 54.8, 109.4, 122.8, 137.9, 142.7, 163.7, 165.8. Anal. Calcd for $C_7H_6BrNO_3$ (232.0): C, 36.26; H, 2.61; N, 6.04. Found: C, 36.23; H, 2.67; N, 6.21 %.

Methyl 2-bromo-6-methoxynicotinate (10). To a stirred solution of 2-bromo-6-methoxynicotinic acid **16** (1 g, 4.3 mmol) and 3 drops of DMF in dry CH_2Cl_2 (20 ml) was slowly added oxalyl chloride (462 µL, 5.4 mmol) at 0°C. The mixture was stirred at room temperature for 1 h and solvents were removed *in vacuo*. Dry methanol (30 ml) was then added at 0°C and the resulting mixture was stirred for 2 h at room temperature. Methanol was removed *in vacuo* and CH_2Cl_2 (30 ml) was added. The organic phase was washed with water (3x15 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the ester **10** (973 mg, 92 %) as white solid, mp= 54-55 °C; IR (KBr) ν 1247, 1586, 1724, 2952; ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3H), 3.93 (s, 3H), 6.93 (d, 1H, *J* = 8.5 Hz), 7.99 (d, 1H, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 42.5, 54.7, 109.3, 121.1, 139.7, 142.4, 164.5, 165.1; Anal. Calcd for $C_8H_8BrNO_3$ (246.0): C, 39.05; H, 3.28; N, 5.69. Found: C, 39.11; H, 3.32; N, 5.71 %.

Preparation of the cyclopenta[b]pyridin-2,5-dione (1)

(*E*)-Methyl 6-methoxy-2-(3-methoxy-3-oxoprop-1-enyl)nicotinate (9). A degassed mixture of methyl 2-bromo-6-methoxynicotinate (**10**, 0.30 g, 1.2 mmol), methyl acrylate (293 µl, 3.3 mmol), allylpalladium chloride dimer $Pd_2(allyl_2Cl_2)$ (24 mg, 0.065 mmol), P(*o*-Tol)$_3$ (40 mg, 0.13 mmol), Na_2CO_3 (320 mg, 3.0 mmol), toluene (2.53 ml) and dimethyl acetamide DMA (0.84 ml) was heated in a sealed tube at 115°C for 5 h. The reaction mixture was filtrated though Celite and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc /

Petrol 3:7) to give **9** (296 mg, 82%) as a yellow solid, mp= 112-113°C; IR (KBr) ν 1132, 1243, 1482, 1589, 1737, 2961, 3012, 3097; ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 3.90 (s, 3H), 3.99 (s, 3H), 6.72 (d, 1H, *J* = 8.6 Hz), 7.11 (d, 1H, *J* = 15.2 Hz), 8.11 (d, 1H, *J* = 8.1 Hz), 8.57 (d, 1H, *J*=15.2 Hz); ^{13}C NMR ($CDCl_3$) δ 52.2, 52.8, 54.2, 112.4, 119.7, 125.2, 140.9, 141.8, 152.8, 164.9, 166.5, 167.6; Anal. Calcd for $C_{12}H_{13}NO_5$ (251.2): C, 57.37; H, 5.22; N, 5.58. Found: C, 57.43; H, 5.34; N, 5.61 %.

Methyl 6-methoxy-2-(3-methoxy-3-oxopropyl)nicotinate (17). A degassed suspension of 10 % Pd/C (60 mg, 0.06 mmol) in a solution of 9 (150 mg, 0.6 mmol) in MeOH (10 ml) was vigorously stirred for 3 h at room temperature under H_2 (1 bar). The reaction mixture was filtered though a short pad of Celite and concentrated *in vacuo* to give 17 (141 mg, 93 %) as a yellow liquid; IR (KBr) ν 1021, 1248, 1595, 1723, 2962; ^{1}H NMR ($CDCl_3$) δ 2.77 (t, 2H, *J* = 7.0 Hz), 3.47 (t, 2H, *J* = 7.0 Hz), 3.63 (s, 3H), 3.83 (s, 3H), 3.88 (s, 3H), 6.53 (d, 1H, *J* = 8.7 Hz), 8.06 (d, 1H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 30.2, 30.7, 50.4, 52.6, 106.9, 116.6, 140.4, 159.9? 163.8, 165.5, 172.9; Anal. Calcd for $C_{12}H_{15}NO_5$ (253.2): C, 56.91; H, 5.97; N, 5.53. Found: C, 56.75; H, 6.04; N, 5.66 %.

Methyl 2-methoxy-5-oxo-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-6-carboxylate (18). Sodium methoxide (81 mg, 1.5 mmol) in THF (5 ml) was added to a solution of 17 (250 mg, 1 mmol) in dry THF (8 ml) under N_2 and the mixture was refluxed for 2 h. The pH was then adjusted to 5 by adding aq. HCl (2*M*) before extraction of the product with CH_2Cl_2 (2x15 ml). The combined organic layers was washed with aq. Na_2CO_3 (10%, 5 ml), sat. aq. NH_4Cl (5 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (EtOAc / petrol 3:7) to give 18 (166 mg, 75 %) as a beige solid, mp= 81-82 °C; IR (KBr) ν 1021, 1250, 1439, 1595, 1736, 2960;^{1}H NMR ($CDCl_3$) δ 3.29-3.31 (m, 1H), 3.45-3.50 (m, 1H), 3.70-3.74 (m, 1H), 3.73 (s, 3H), 4.00 (s, 3H), 6.68 (d, 1H, *J*= 8.7 Hz), 7.82 (d, 1H, *J*= 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 33.3, 53.1, 53.2, 54.9, 112.2, 123.3, 135.1, 169.7, 169.8, 175.1, 196.5.

6,7-Dihydro-1*H*-cyclopenta[*b*]pyridine-2,5-dione (1). A solution of **18** (100 mg, 0.45 mmol) in aq. HCl (5 M, 2 ml) was refluxed for 3 h. The mixture was cooled to room temperature and the pH was adjusted to 5 by adding aq. K_2CO_3 (2 M). The product was extracted with EtOAc (5x15mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* to give **1** (56 mg, 84 %) as a beige solid, mp> 260°C; IR (KBr) ν 3085, 2924, 1675-1653, 1427, 1105; ^{1}H NMR (DMSO) δ 2.56 (m, 2H), 2.94 (t, 2H, *J* = 5.1 Hz), 6.31 (d, 1H, *J* = 9.4 Hz), 7.58 (d, 1H, *J* = 9.4 Hz), 12.6 (s, 1H) ; ^{13}C NMR (DMSO) δ 24.5, 34.7, 116.3, 119.2, 134.1, 164.1, 169.5, 199.3; Anal. Calcd for $C_8H_7NO_2$ (149.1): C, 64.43; H, 4.73; N, 9.39. Found: C, 64.42; H, 4.83; N, 9.23 %.

References and Notes

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